Epigenetic determinants of the early life programming of disease

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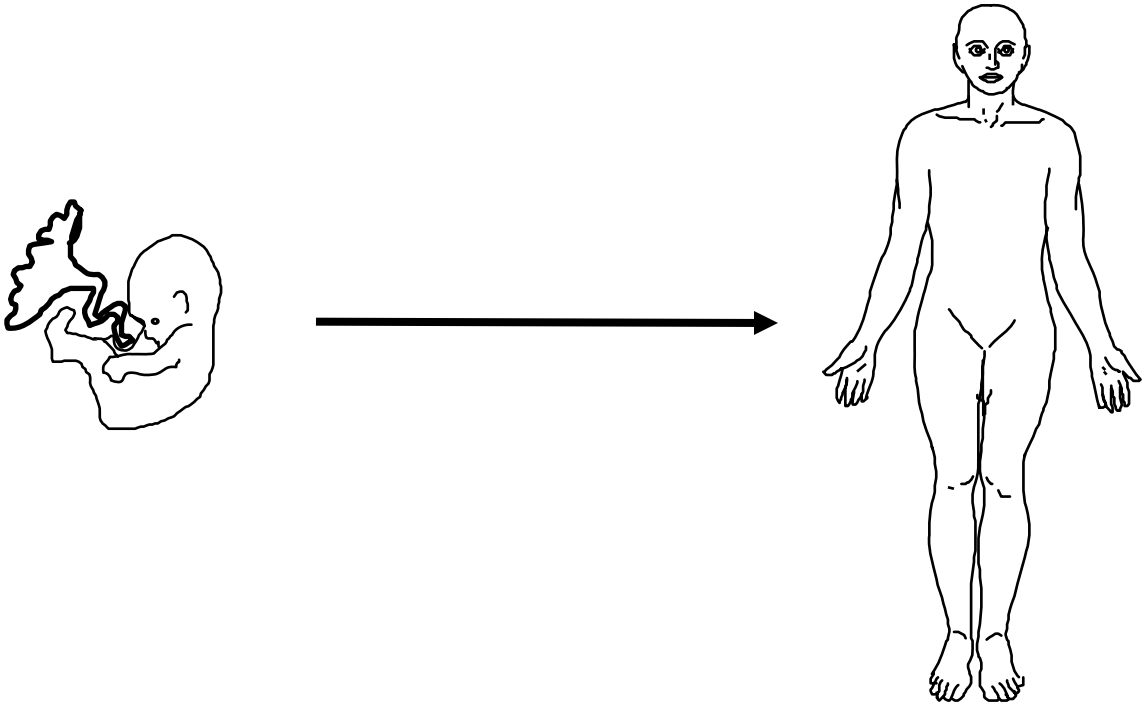
University of Edinburgh

Low birth weight

Adult disease



Glucose intolerance

Hypertension

Insulin resistance syndrome

HPA axis activation

Hertfordshire studies

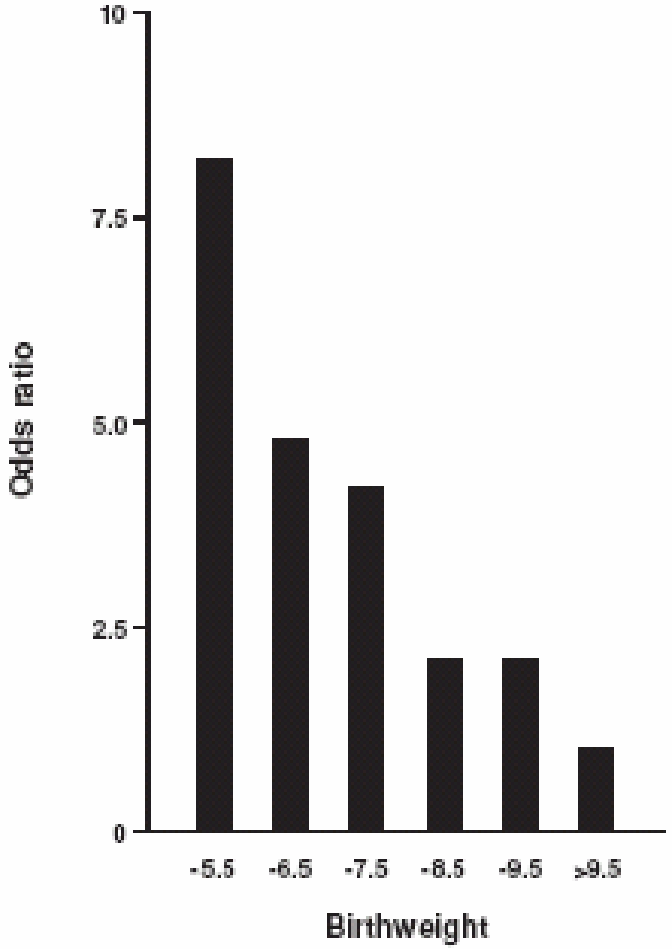
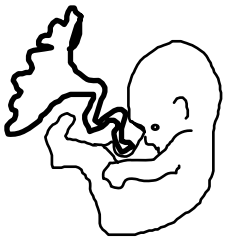


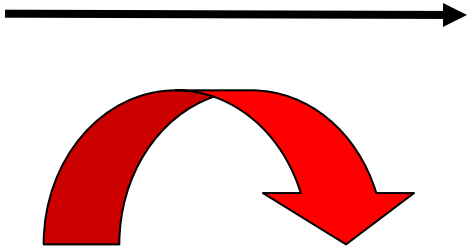
Fig. 1 Odds ratio for impaired glucose tolerance or type 2 diabetes according to birth weight among 370 men aged 64 years born in Hertfordshire (adjusted for adult body mass index).

Hales and Barker 1991

Low birth weight

Adult disease





OBESITY

Glucose intolerance

Hypertension

Insulin resistance syndrome

HPA axis activation

Early life origins of disease – ‘programming’

- Action of a factor at a specific developmental ‘window’ leads to permanent effects on tissue growth and development and predisposition to later disease

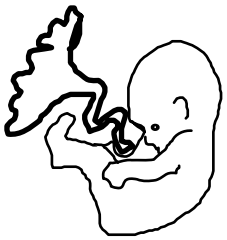
- Endocrine disruptors / endocrine active compounds

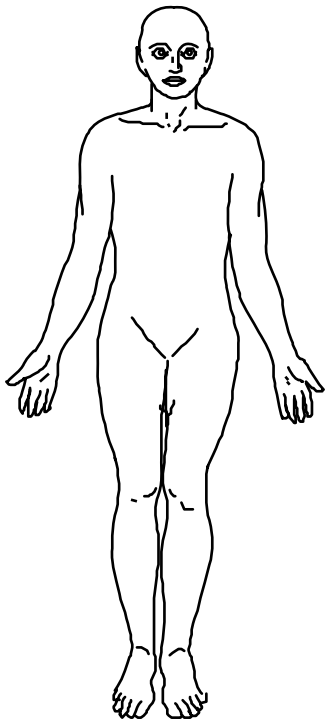
- Timing and / or duration of exposure

Low birth weight

Adult disease

Malnutrition





Glucose intolerance

Hypertension

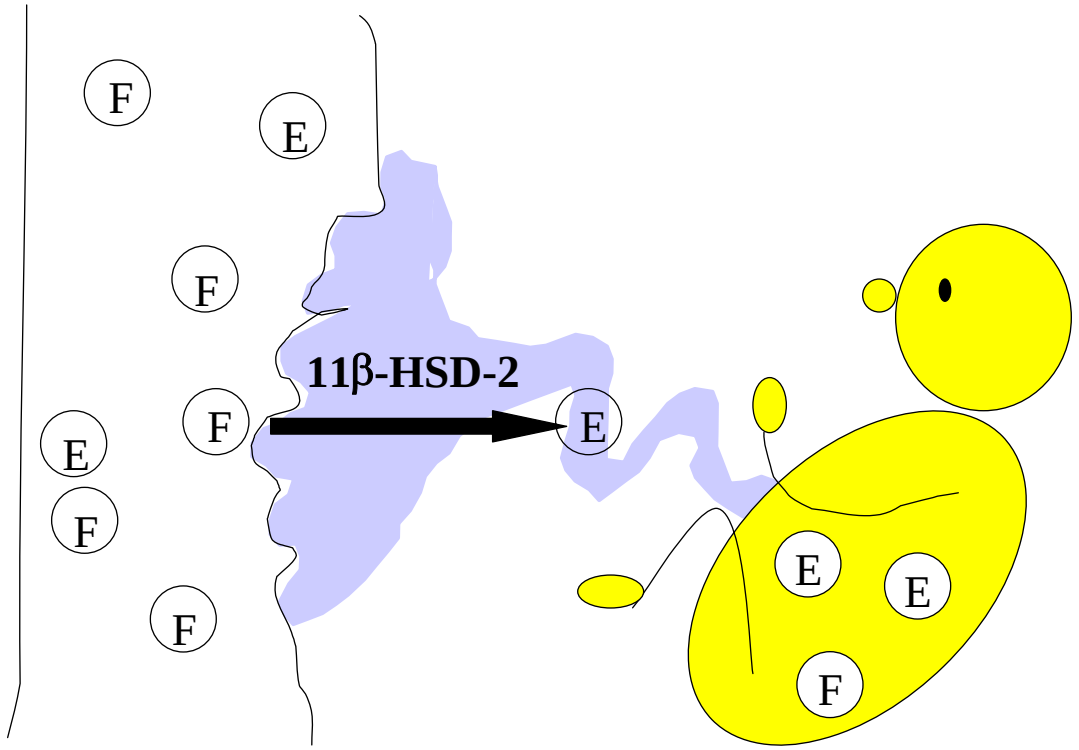
Insulin resistance syndrome

HPA axis activation

Glucocorticoids

Genes

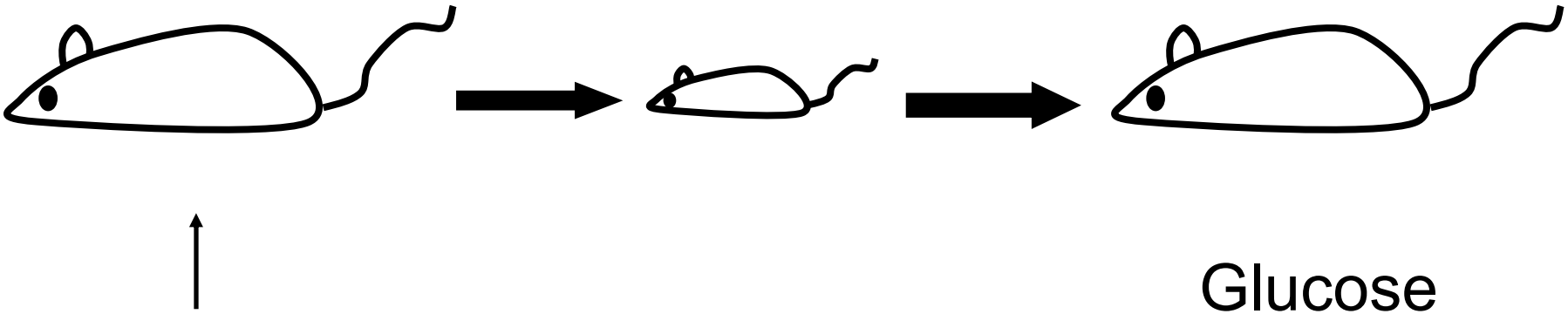
Glucocorticoids and the placenta



Maternal circulation

Fetal circulation

Low birth
weight



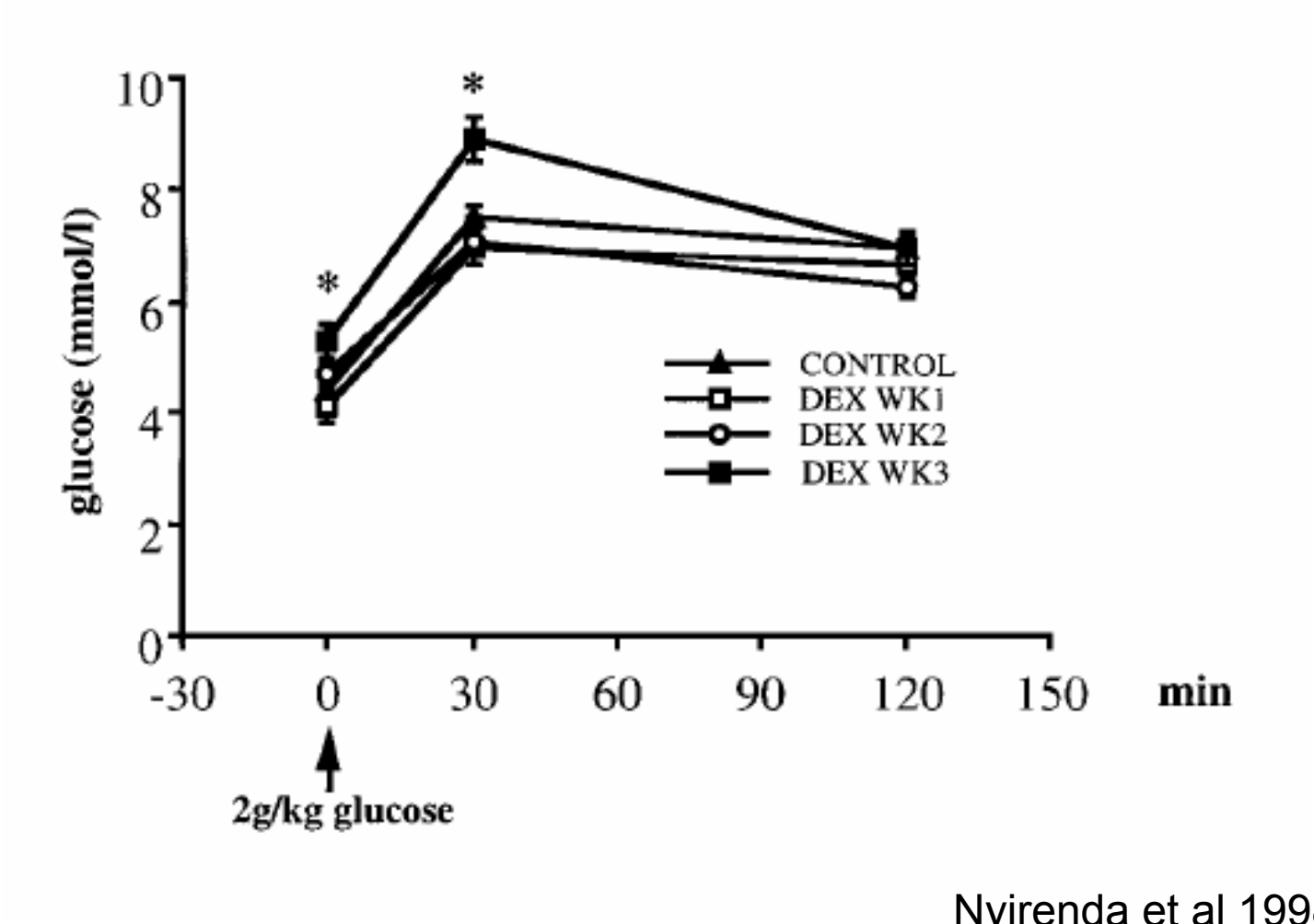
Dexamethasone

Glucose
intolerance

HPA

Hypertension

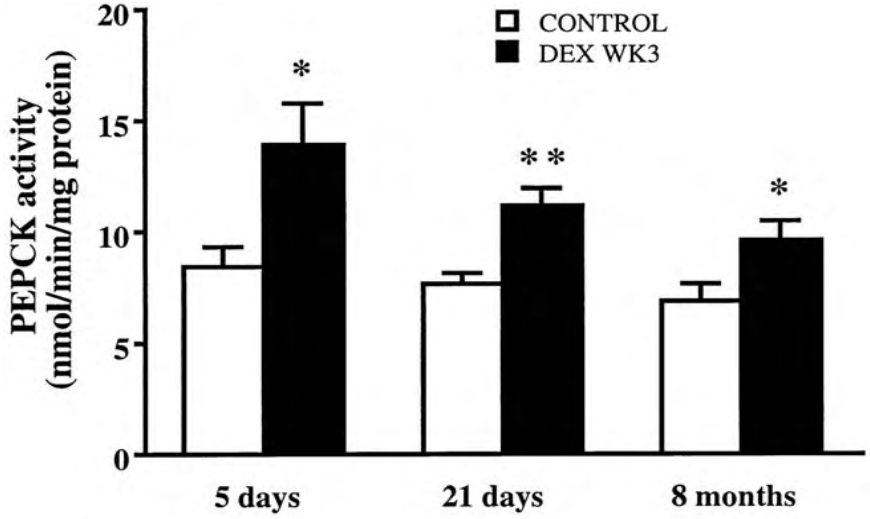
Glucose tolerance



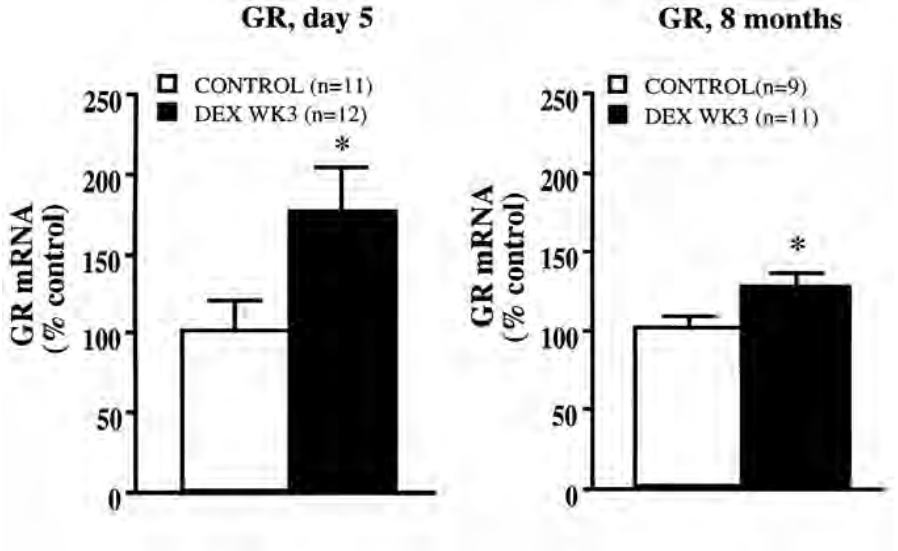
Nyirenda et al 1998

Liver

Hepatic PEPCK



Hepatic GR

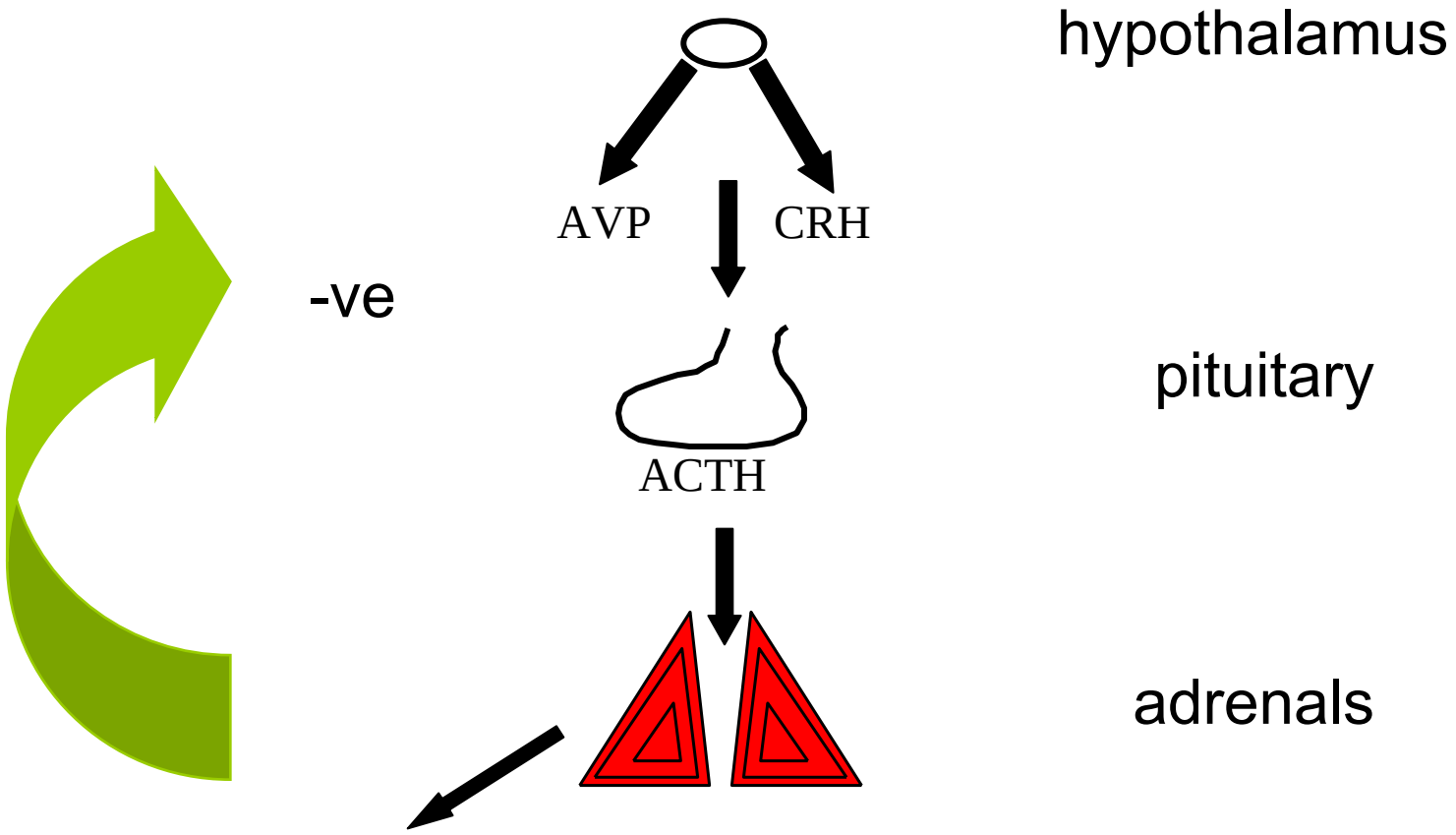


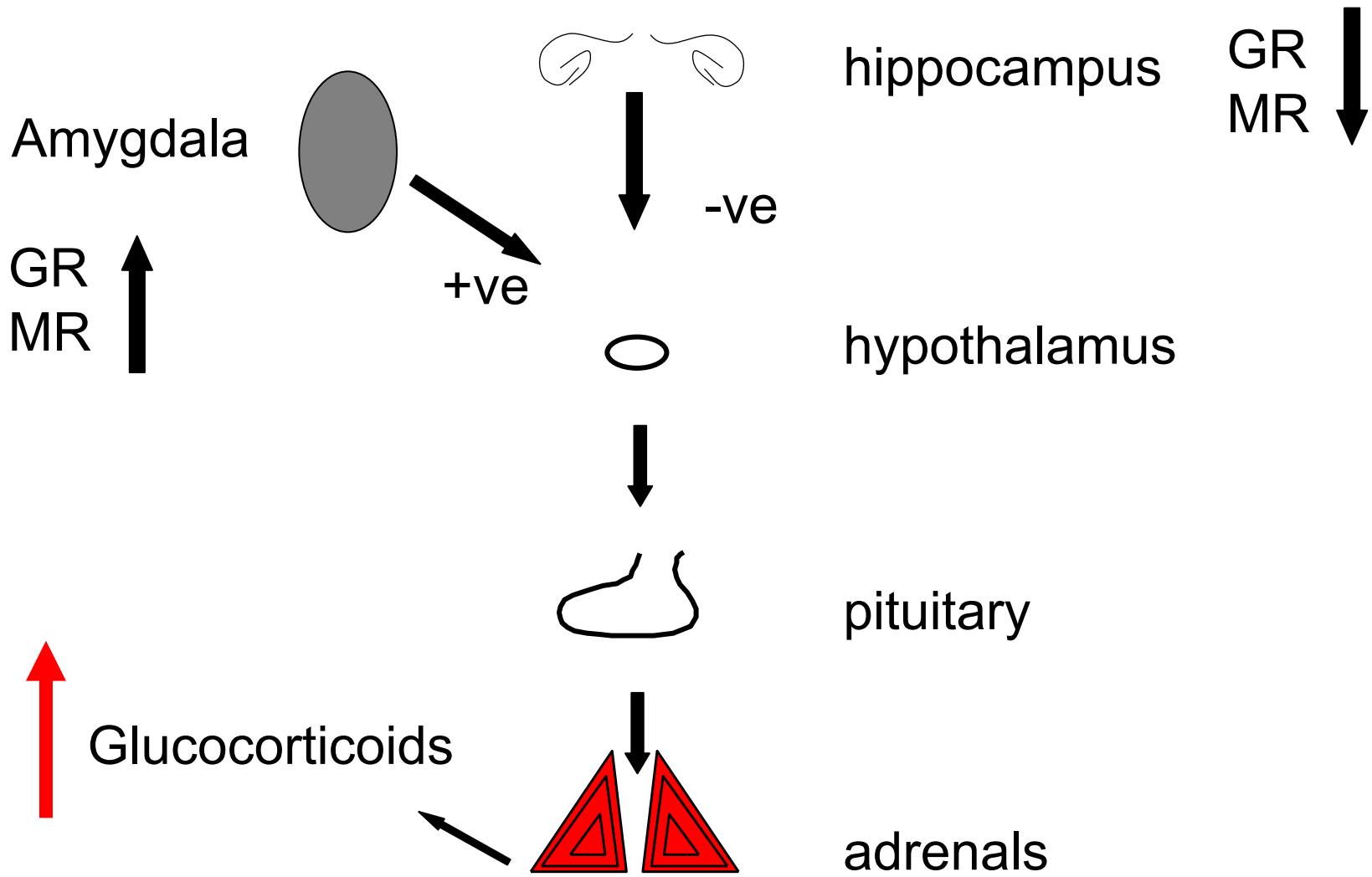
Nyirenda et al

Muscle & fat

- Depot-specific increase in muscle GR (Cleasby et al)
- Increased muscle GR associated with insulin resistance & hypertension in men (Reynolds et al)
- Altered adipose GR expression & decreased fatty acid uptake (Cleasby et al)

Brain – HPA axis




Amygdala
GR
MR
+ve
hippocampus
GR
MR
-ve
hypothalamus
pituitary
Glucocorticoids
adrenals

Programming mechanisms

- Modification of gene expression (tissue specific)
  - Direct receptor stimulation / inhibition
  - Altered gene expression / transcription factors
- Altered circulating hormone levels
  - Altered hormone synthesis / metabolism
- Other mechanisms
  - Altered cell number
  - Altered appetite / activity levels

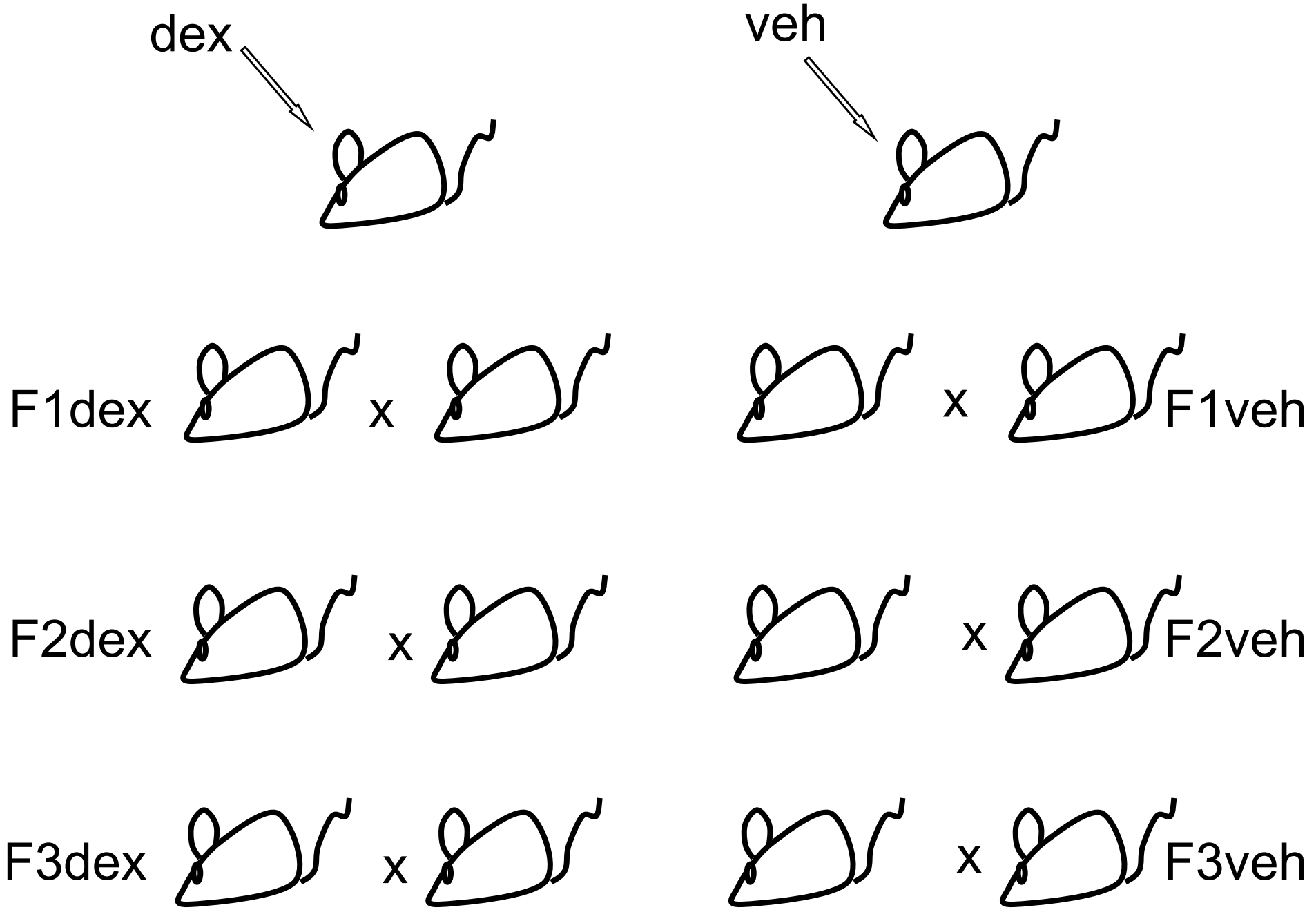
Intergenerational effects

- ‘Intergenerational cycle of growth failure’ in the developing world

- Unicef - ‘The State of the World’s Children’ 1998
  - Young girls who grow poorly become stunted women and are more likely to give birth to low birth weight babies. If these infants are girls they are likely to continue the cycle by being stunted in adulthood and so on

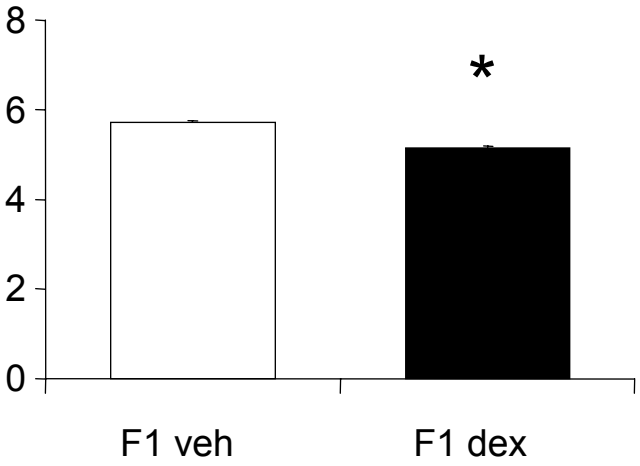
Developed countries?

- Baird (Aberdeen, UK) 1950s onwards
- Emanuel (UK 1958 birth cohort)
  - Matrilineal multigenerational effect
  - Relationship between birth weight, intrauterine growth rate and adult height
- Well recognised intergenerational effects on other cardiovascular risk factors

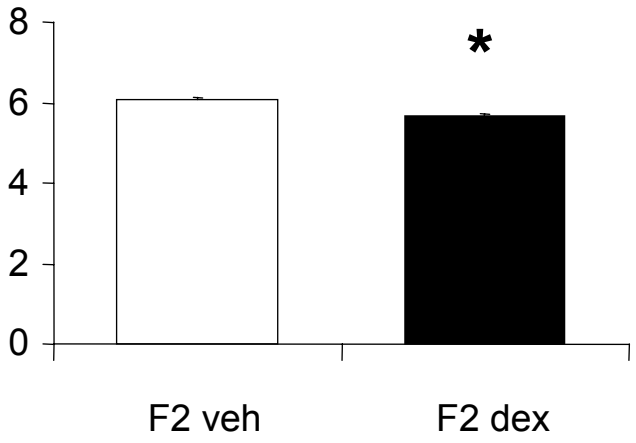

dex
veh
F1dex
x
x
F1veh
F2dex
x
x
F2veh
F3dex
x
x
F3veh

Weight (g)

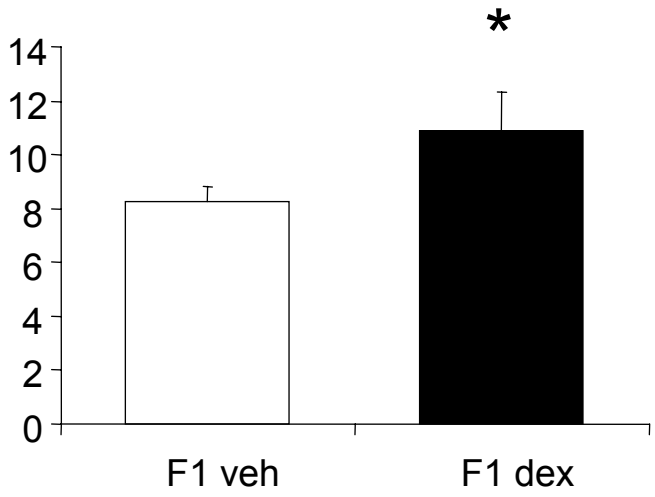
F1

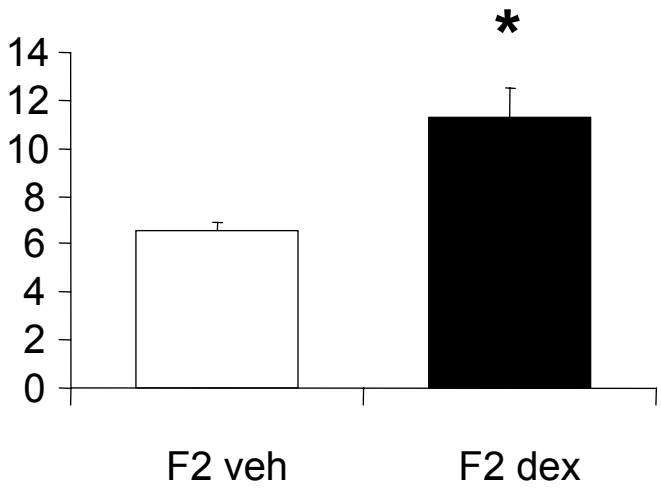


F2

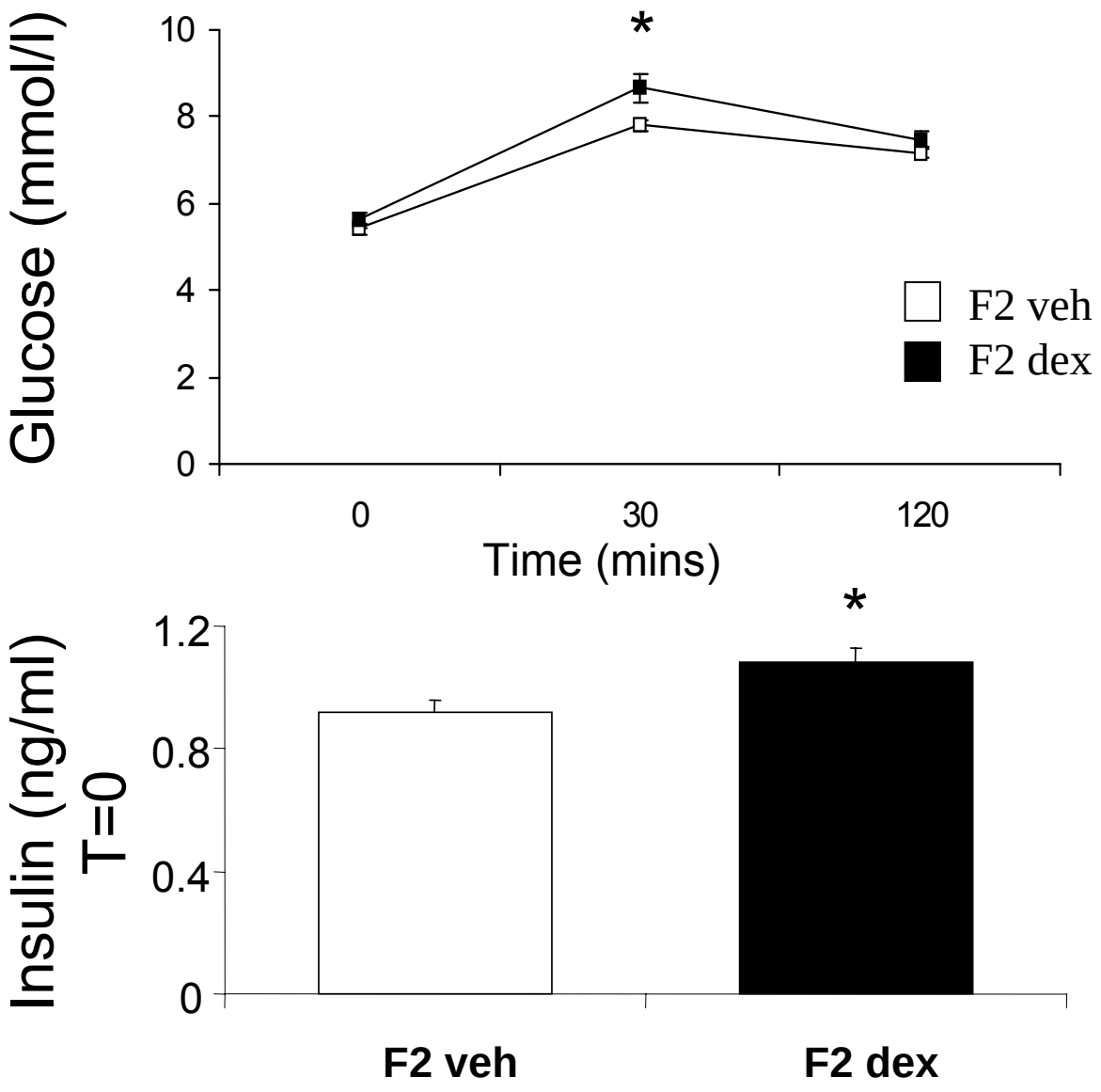


PEPCK (nmol/min)

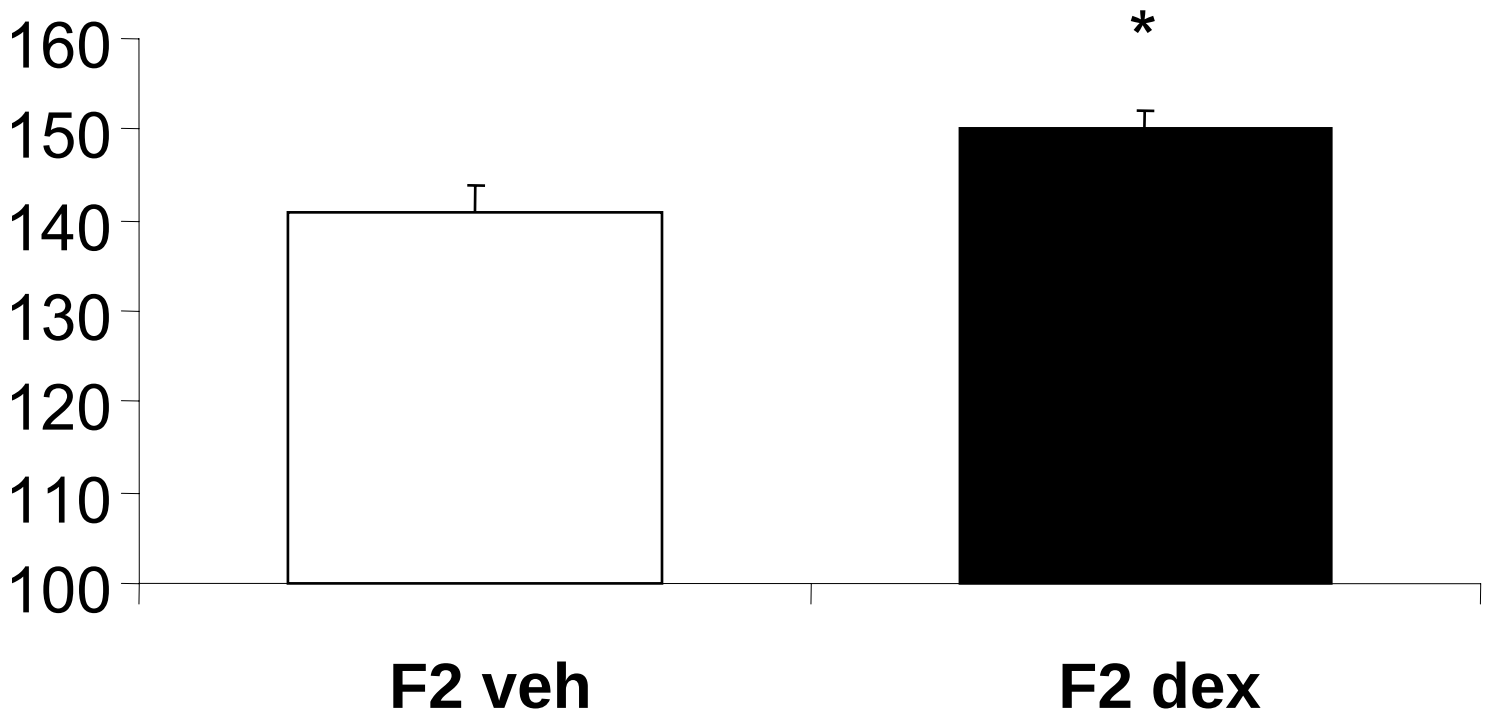


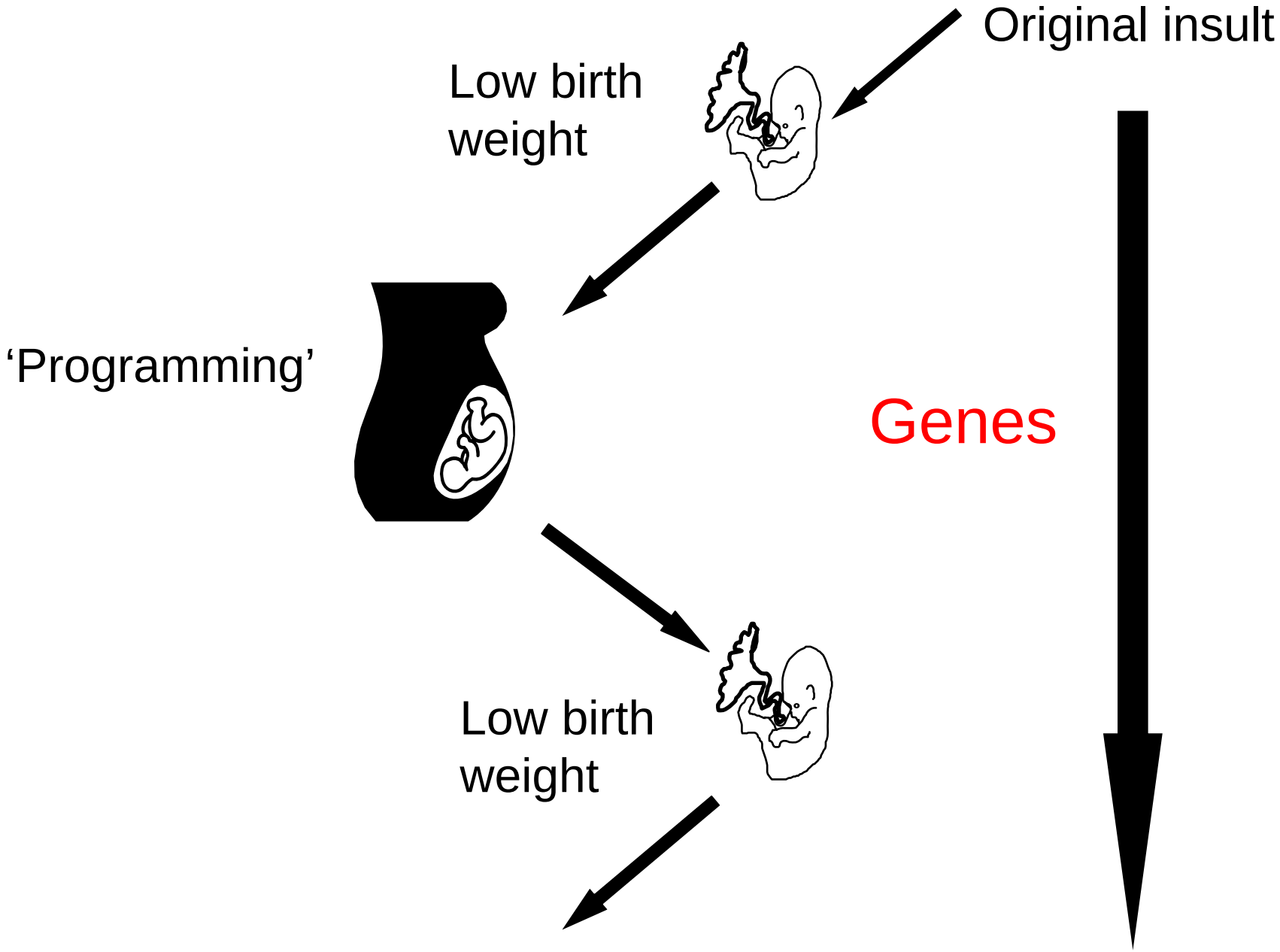


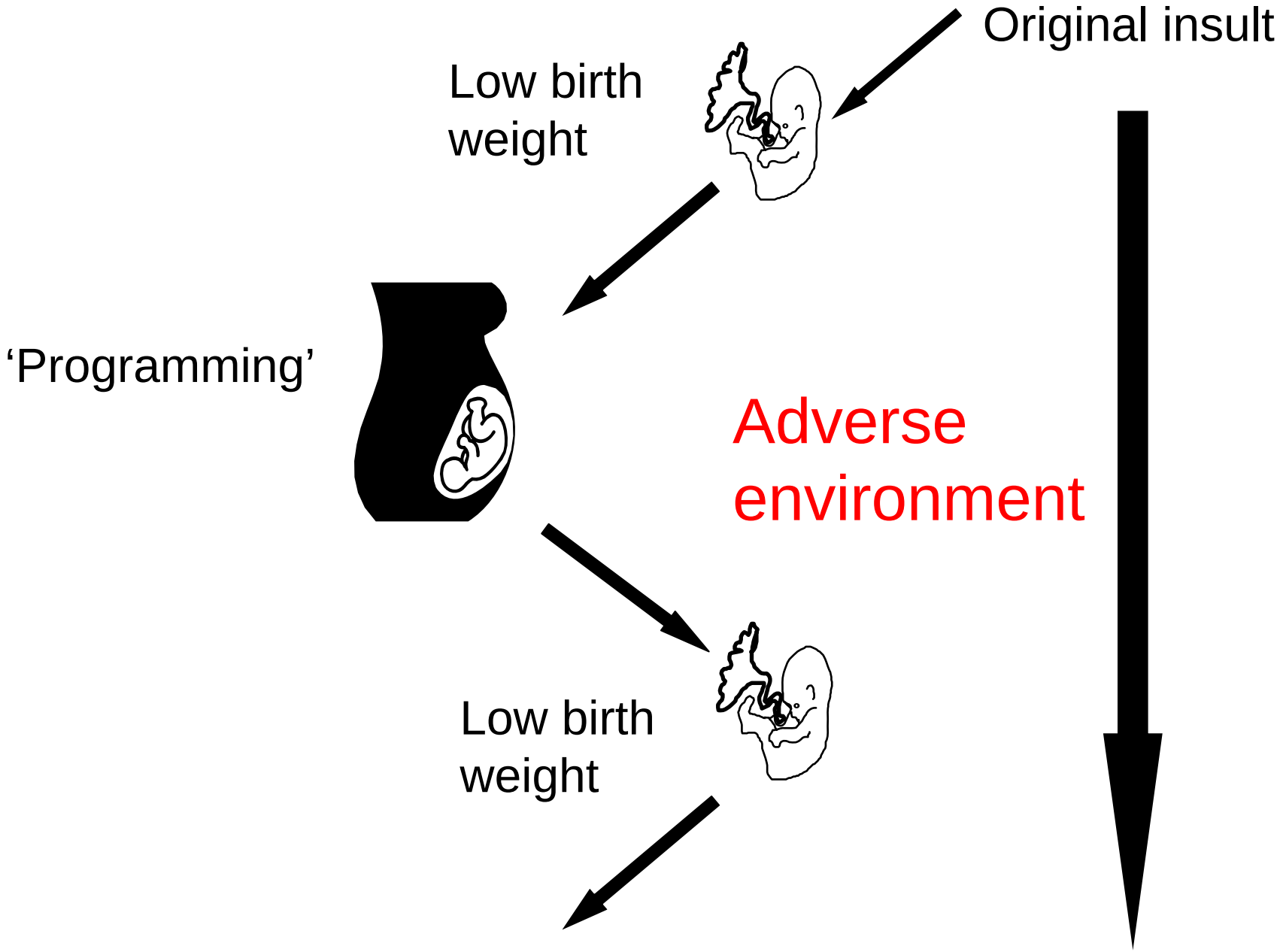
Glucose tolerance in F2 males

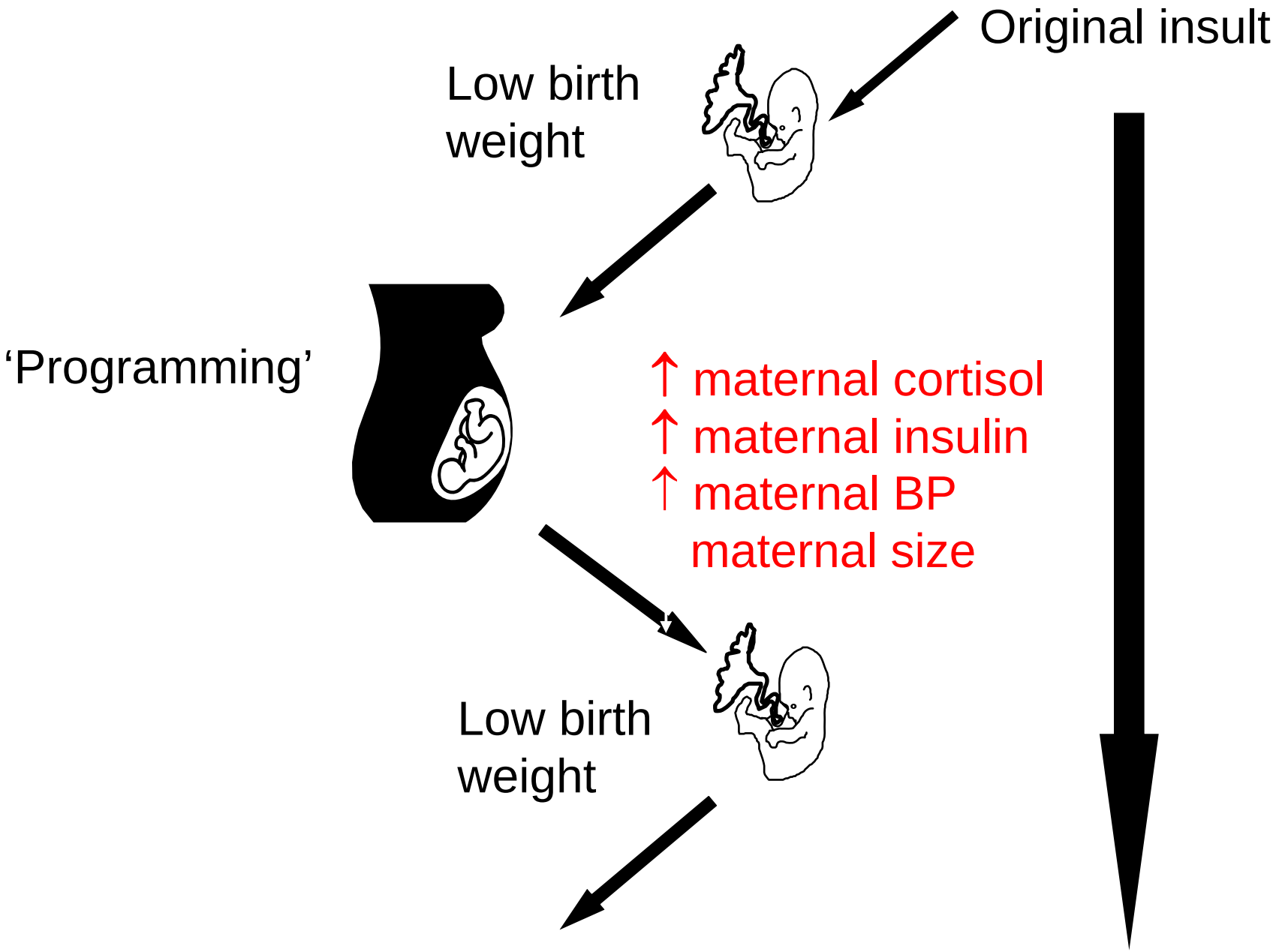


Blood pressure in F2 males




Original insult
Low birth weight
'Programming'
Genes
Low birth weight

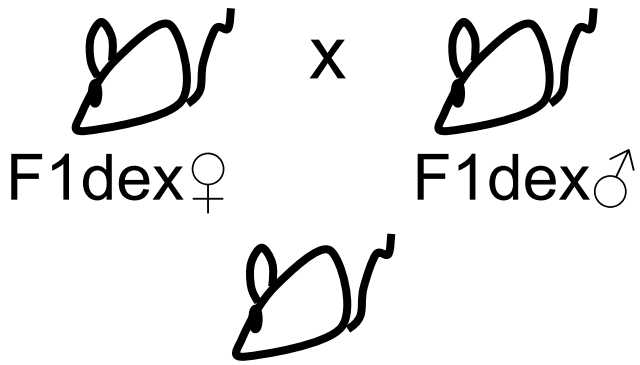

Original insult
Low birth weight
'Programming'
Adverse environment
Low birth weight


Original insult
Low birth weight
'Programming'
↑ maternal cortisol
↑ maternal insulin
↑ maternal BP
maternal size
Low birth weight

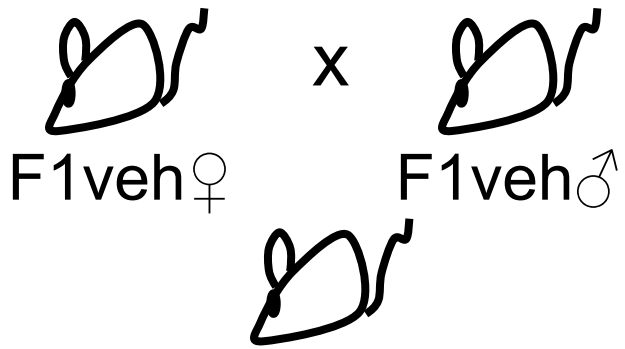
Paternal effects?

- Human studies suggest also paternal effect on transmission diabetes risk etc.

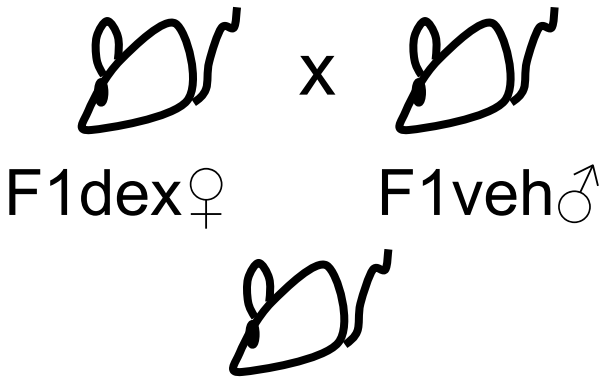
- Överkalix (Kaati 2002, Pembrey 2006)
  - Excess food during paternal grandfather's SGP increased diabetes risk in grandchild and increased mortality risk in grandson
  - Excess food during paternal grandmother's SGP increased mortality RR in granddaughter
  - Poor food supply had opposite effect



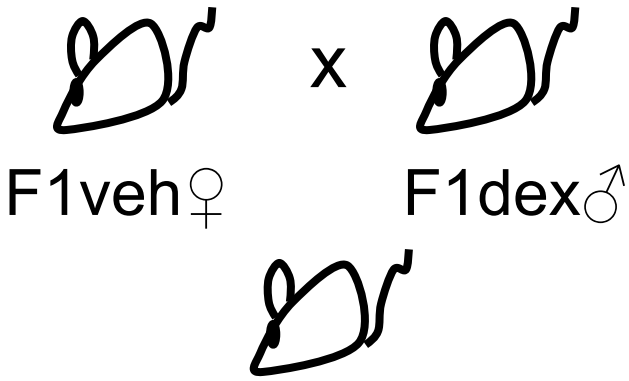
F2 dex/dex



F2 veh/veh

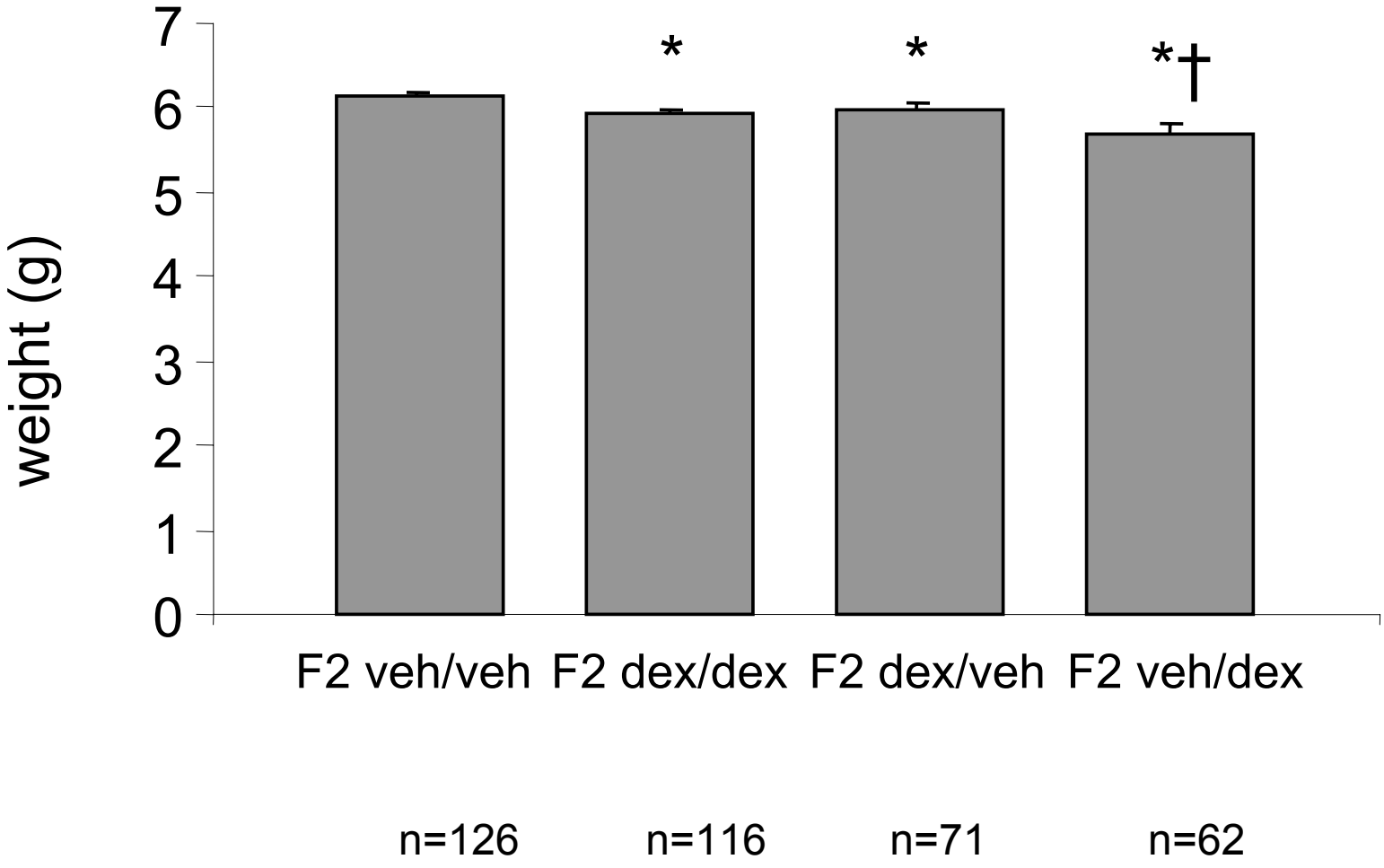


F2 dex/veh

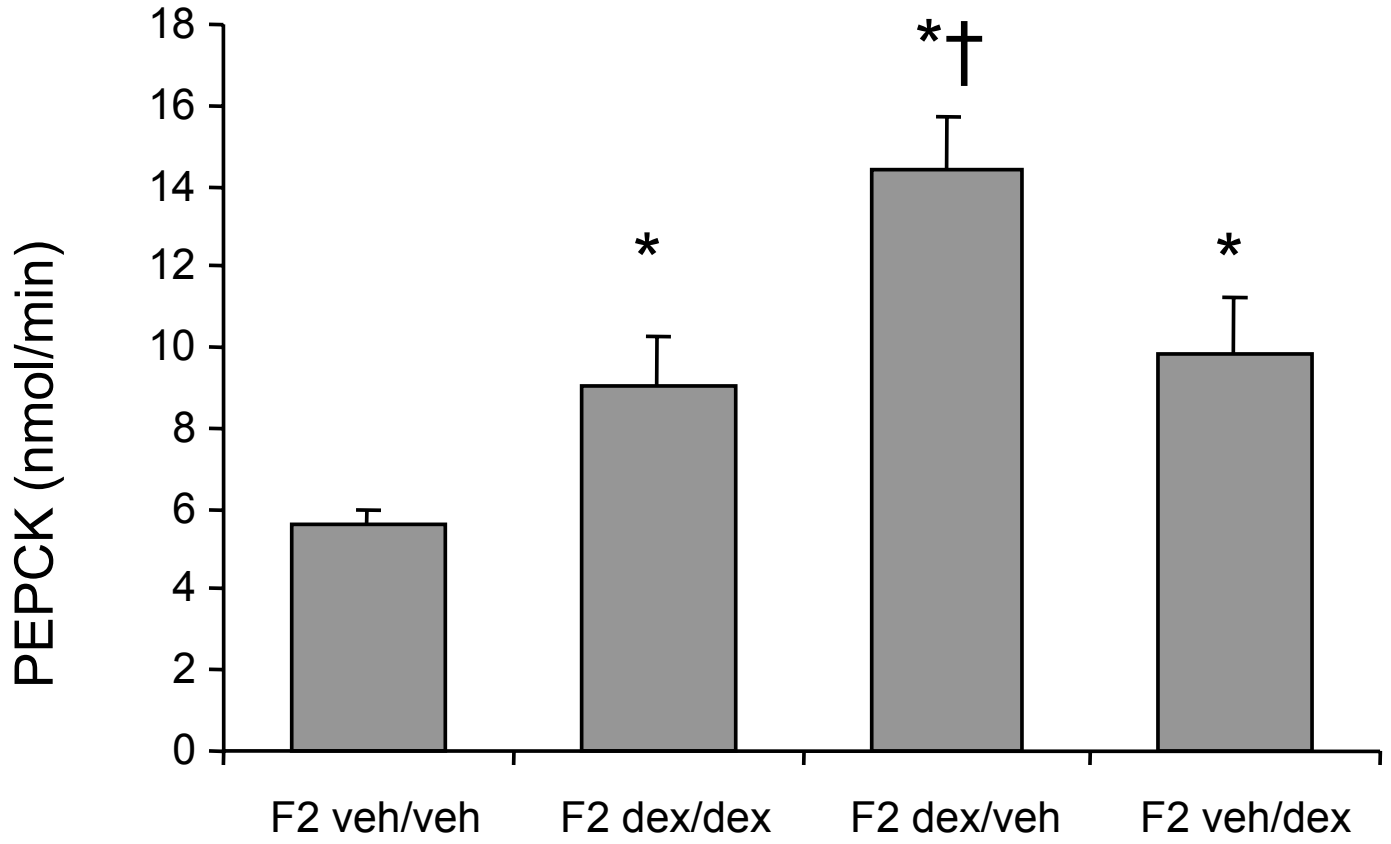


F2 veh/dex

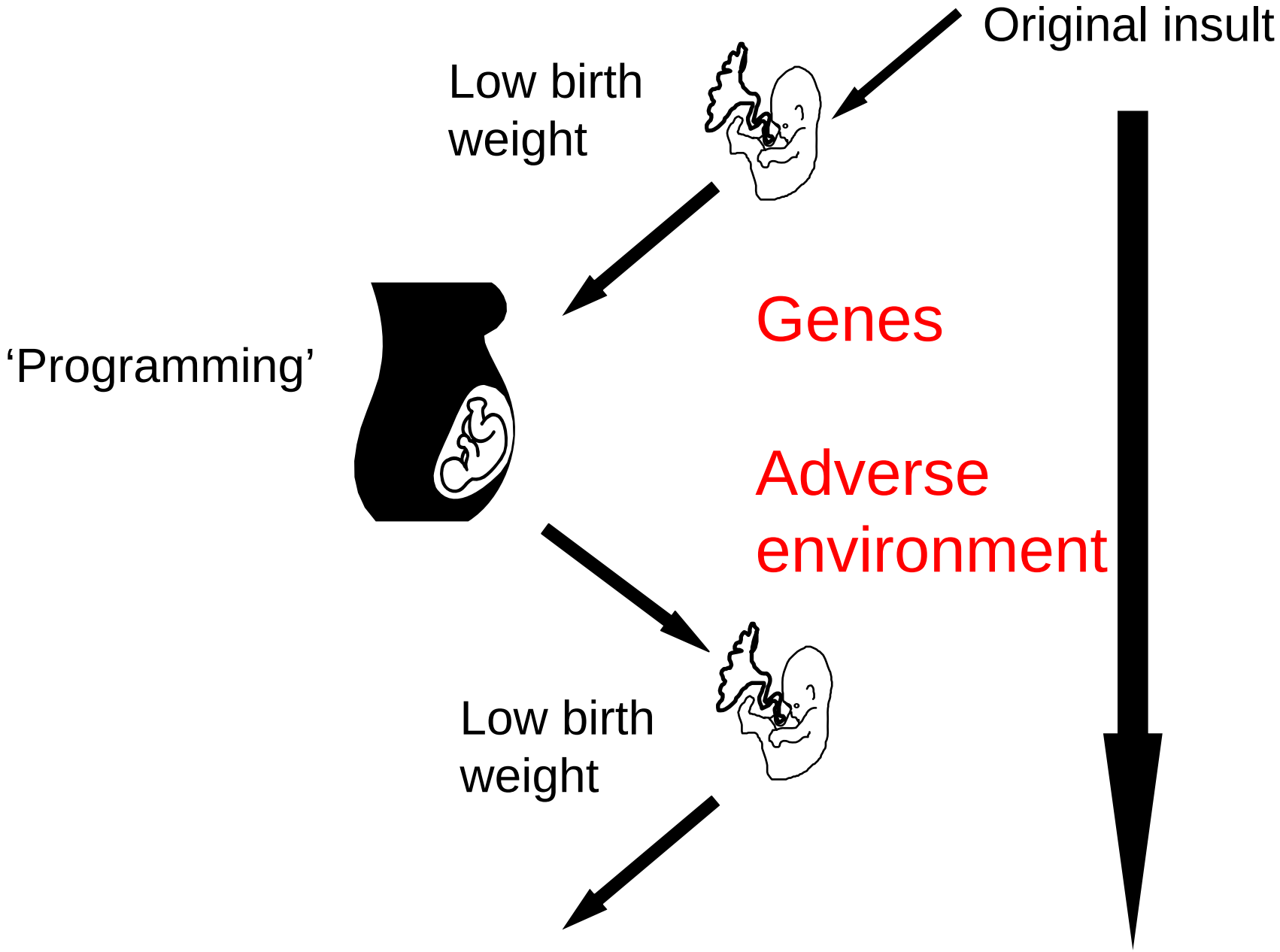
Birth weight

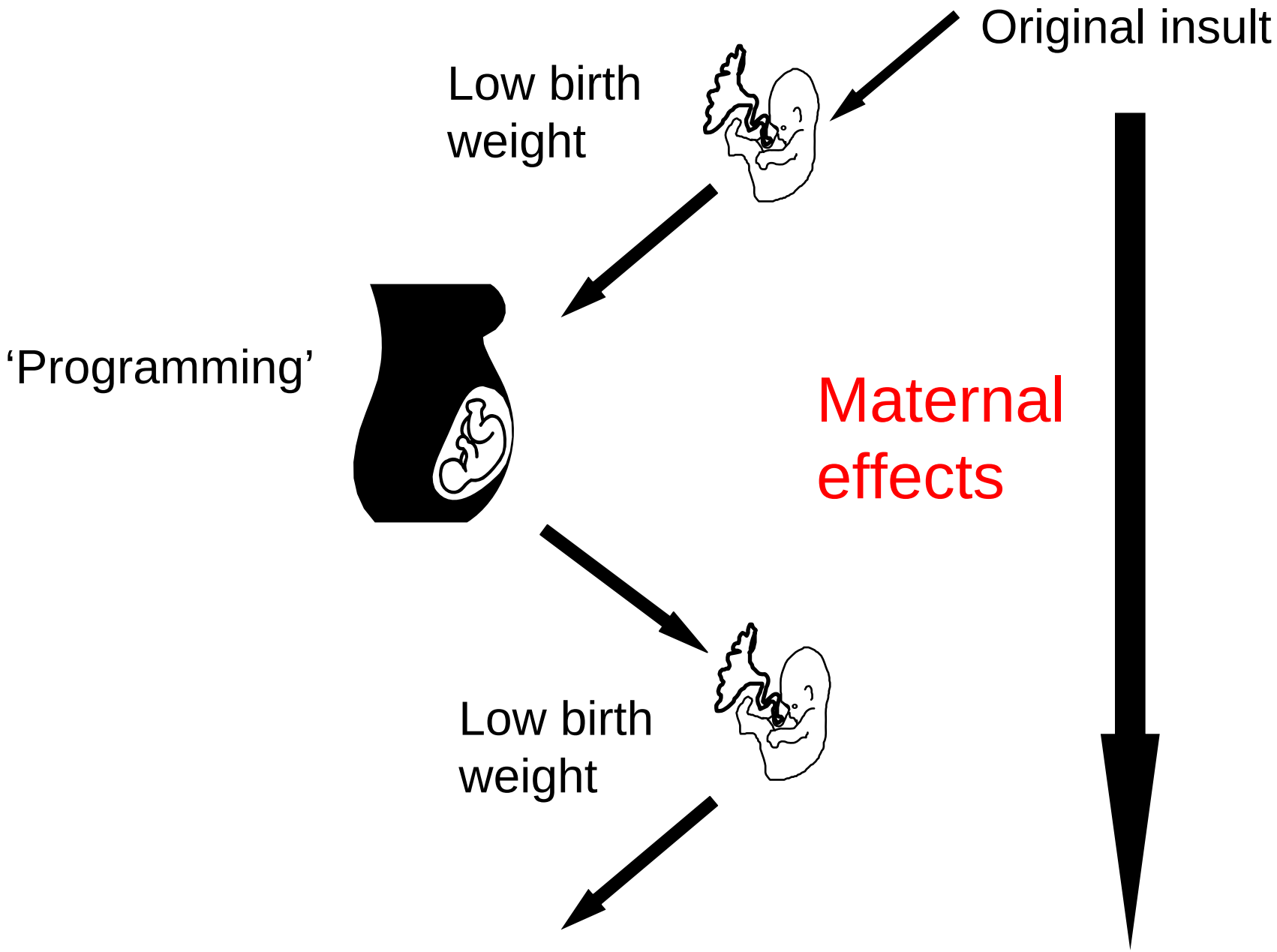


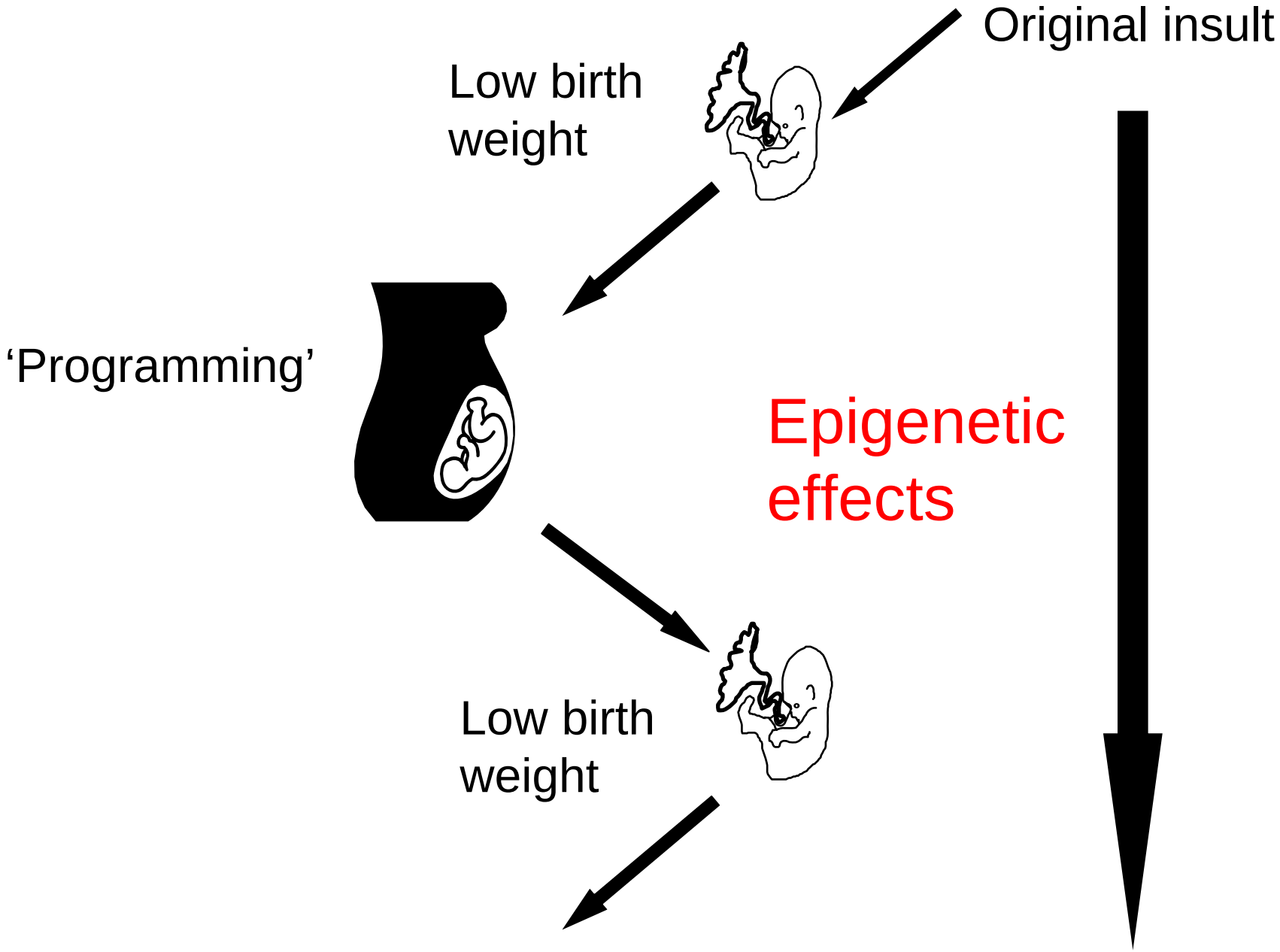
PEPCK activity



Males at 5 weeks, n=7-8 per group


Original insult
Low birth weight
Genes
‘Programming’
Adverse environment
Low birth weight


Original insult
Low birth weight
'Programming'
Maternal effects
Low birth weight


Original insult
Low birth weight
'Programming'
Epigenetic effects
Low birth weight

Epigenetic effects

- Modifications which influence gene expression without changing the DNA sequence

- DNA methylation, modification of histones, expression of non-coding RNAs

- Influence transcriptional activity

- Low protein diet – altered hepatic gene methylation and histone acetylation
- Maternal care - differences associated with altered methylation at hippocampal GR
- Epigenetic modifications at some alleles
  - May be ‘inherited’
  - May be modified by ‘environmental factors’

Agouti yellow (A^{vy}) mice

- A^{vy} allele - IAP inserted at 5' end agouti A allele
- Ectopic agouti transcription initiated from cryptic promoter in A^{vy} IAP
- CpG methylation varies & correlates inversely with ectopic *agouti* expression

Waterland & Jirtle 2003

F0 dietary (methyl donor) supplements
before and during pregnancy

↓

Increase A^{vy} methylation F1 offspring

↓

Shifted towards pseudoagouti phenotype

Second generation effects

- Methyl supplements only during mid-gestation (E8.5-E15.5). No effects on F1 (after somatic epigenotype of A^{vy} set)

- Effects on F2 phenotype - presumably by affecting epigenetic state of A^{vy} in germ line

Cropley et al 2006

Summary

- Many potential mechanisms underpin programming of disease susceptibility
- Many ‘programming’ targets, specific time windows, sex-specific effects
- Epigenetic modifications may be particularly important
- Intergenerational effects

Acknowledgements

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